

Current treatment options and biology of peritoneal mesothelioma: meeting summary of the first NIH peritoneal mesothelioma conference

R. Hassan^{1*}, R. Alexander¹, K. Antman¹, P. Boffetta², A. Churg³, D. Coit⁴, P. Hausner⁵, R. Kennedy⁶, H. Kindler⁷, M. Metintas⁸, L. Mutti⁹, M. Onda¹, H. Pass¹⁰, A. Premkumar¹, V. Roggli¹¹, D. Sterman¹², P. Sugarbaker¹³, R. Taub¹⁴ & C. Verschraegen¹⁵

¹National Cancer Institutes of Health, Bethesda, USA; ²International Agency for Research on Cancer, Lyon, France; ³University of British Columbia, Canada; ⁴Memorial Sloan-Kettering Cancer Center; ⁵University of Maryland; ⁶Texas Tech University Health Sciences Center; ⁷University of Chicago, Chicago, USA; ⁸Osmangazi University, Turkey; ⁹Local Health Unit 11, Vercelli, Italy; ¹⁰Karmanos Cancer Institute; ¹¹Duke University Medical Center; ¹²University of Pennsylvania; ¹³Washington Hospital Center; ¹⁴Columbia University; ¹⁵University of New Mexico, USA

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Peritoneal mesothelioma is a rare cancer of the peritoneum with about 250 new cases diagnosed each year in the United States. It is the second most common site for mesothelioma development and accounts for 10–20% of all mesotheliomas diagnosed in the United States. A meeting sponsored by the NIH Office of Rare Diseases was held in Bethesda, Maryland on September 13 and 14, 2004. The objective of this meeting was to review the epidemiology, biology and current surgical and medical management of peritoneal mesothelioma. In addition, the meeting also discussed clinical and pre-clinical evaluation of novel treatments for mesothelioma as well as ongoing laboratory research to better understand this disease. This report summarizes the proceedings of the meeting as well as directions for future clinical and basic research.

Key words: cancer, mesothelioma, peritoneal

introduction

Malignant peritoneal mesothelioma is a rare neoplasm that develops from the mesothelial cells lining the peritoneum and like pleural mesothelioma is also associated with asbestos exposure in many patients [1]. Only about one-fifth of mesotheliomas occur in the peritoneum. A recent analysis of the Surveillance, Epidemiology, and End Results (SEER) program of the NCI estimated approximately 250 new cases of peritoneal mesothelioma in the United States each year [2]. Though the overall incidence of peritoneal mesothelioma was higher in males than females, a higher proportion of females develop mesothelioma involving the peritoneum compared to males. The best treatment results have been obtained from specialized centers using a combination of tumor debulking and intraoperative chemotherapy. Clearly there is a need to better understand the molecular basis of this disease as well as develop guidelines for treating such patients.

A meeting was held in Bethesda, Maryland, on September 13–14th, 2004, sponsored by the National Institutes of Health, Office of Rare Disease and chaired by Dr Raffit Hassan of the National Cancer Institute. The meeting was organized into five

sessions that dealt with: (1) genetics and epidemiology of mesothelioma, (2) pathologic and radiologic aspects of peritoneal mesothelioma, (3) surgical management of peritoneal mesothelioma, (4) medical management of peritoneal mesothelioma and (5) clinical and pre-clinical evaluation of novel treatments for mesothelioma. Each session consisted of lectures by experts followed by an open discussion. This article will highlight some of the information presented at the meeting. The meeting also included a presentation by Christopher E. Hahn of the Mesothelioma Applied Research Foundation (MARF), a national nonprofit organization working on mesothelioma who mentioned that MARF has awarded more than \$1.3 million for research since being founded in 1999 and therefore represents a significant new funding source for mesothelioma researchers.

Dr Karen Antman (National Cancer Institute, USA) the keynote speaker for the meeting provided an overview of mesothelioma in general with a focus on peritoneal mesothelioma. She mentioned that because of its non-specific symptoms, peritoneal mesothelioma is often diagnosed late, and in women is often confused with ovarian cancer. However, improvements in immunohistochemistry now allow pathologists to make a more accurate diagnosis. Because of the difficulty of conducting randomized trials in a rare disease such as peritoneal mesothelioma most of the information regarding its management is obtained from single institution

*Correspondence to: Dr R. Hassan, Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, 37 Convent Drive, Room 5116, Bethesda, MD 20892–4264 USA. Tel: +1 (301) 451-8742; Fax: +1 (301) 402-1344; E-mail: hassanr@mail.nih.gov

Phase I/II studies. Some of these studies show that surgical debulking and intraperitoneal chemotherapy result in longer than expected overall survival. However, selection bias could account for the observed survivals. Dr Antman stated that national and international collaborations would be necessary to perform large trials to define the optimal treatment of peritoneal mesothelioma. Dr Antman also touched on some of the issues regarding peritoneal mesothelioma: Does complete resection improve survival? Why do women survive longer than men? What chemotherapy to use? Does the better prognosis of epithelial compared to sarcomatoid peritoneal mesothelioma suggest two different diseases? Some of these questions were addressed by speakers in the conference.

genetics and epidemiology of peritoneal mesothelioma

This session was chaired by **Dr Kenneth Cantor (National Cancer Institute, USA)** and **Dr Courtney Broaddus (University of California San Francisco, USA)** and included presentations regarding the genetics and epidemiology of mesothelioma with an emphasis on peritoneal mesothelioma.

This session began with a presentation by **Dr Harvey I. Pass (Karmanos Cancer Institute, USA)**, who described the importance of genomic and proteomic in mesothelioma as an aid in early detection/monitoring, prognostication, and new target drug discovery. He presented work by his group using gene arrays to identify novel combinations of known and unknown genes which can reliably predict progression and survival in patients with pleural mesothelioma who had surgical cytoreduction [3]. In addition, proteomic data from his lab has identified a combination of 4–6 biomarkers in malignant mesothelioma (MM) pleural effusion that can help distinguish benign and non-MM effusions from MM pleural effusions. Dr Pass also mentioned that their preliminary laboratory studies suggest that soluble mesothelin related (SMR) protein could potentially help monitor MM disease status as well as be an early detection serum marker [4]. Dr Pass felt that such genomic and proteomic studies are likely to be important in peritoneal mesothelioma as well.

Dr Paolo Boffetta (International Agency for Research on Cancer, Lyon, France) discussed the epidemiology of peritoneal mesothelioma. His studies have found that although the geographical patterns of peritoneal mesothelioma parallel pleural mesothelioma the rates are consistently lower. Overall, Europe experiences 1 to 2 cases of peritoneal mesothelioma per million per year. His studies have also shown that while in high-risk, industrialized countries the ratio between pleural and peritoneal mesotheliomas is on the order of 10–30:1, in low-risk countries the ratio is 3–10:1, suggesting that heavy exposure to asbestos increases predominantly the risk of pleural mesotheliomas. Dr Boffetta mentioned that in studies with an adequate number of cases, a strong association has been found between the estimated occupational exposure to asbestos and the risk of peritoneal mesothelioma [2, 5]. Also, cases of peritoneal mesothelioma have been reported following exposure to erionite and thorotrast [6].

Dr Muzaffer Metintas (Osmangazi University, Turkey) described the Turkish experience with malignant mesothelioma

that is endemic in some rural parts of Anatolia, Turkey. He presented data from his studies that have shown that the high risk of mesothelioma in this region is due to environmental exposure to asbestos-contaminated soil mixtures [7]. Mineral analysis of these white-soil samples identified contamination predominantly with tremolite. In addition, erionite exposure has caused mesothelioma in three villages of the Cappadocia region. Cumulative low exposure to the asbestos fibers has resulted in a higher-than-average incidence of malignant mesotheliomas with a mean latent period of 56 years. The country of Turkey represents a special case of high incidence of malignant mesothelioma due to environmental exposure. In the year 2002, it was estimated that more than 250,000 people have been exposed to asbestos in villages, and about 3,000 villagers to erionite in Cappadocia. Researchers expect Turkey to experience 600 new cases of malignant mesothelioma annually until 2030. Because of epidemiologic work by Turkish researchers the use of ‘white soil’ containing asbestos fibers for housing construction has declined significantly.

pathologic and radiologic aspects of peritoneal mesothelioma

This session was chaired by **Dr Elliott Kagan (Uniformed Services University of the Health Sciences, USA)** and **Dr Jorge Carrasquillo (National Institutes of Health, USA)** and included presentations regarding imaging studies as well as pathology of this disease.

This session started with a presentation by **Dr Ahalya Premkumar (National Institutes of Health, USA)**. She mentioned that CT is the method of choice for imaging this tumor, although it requires the use of oral and intravenous contrast agents to distinguish tumors from nearby tissues [8]. CT scanning can reveal thickening, infiltration and tumor nodules involving the peritoneum, mesentery and omentum. Other findings include ascites, masses involving the bowel serosa, extensions into the liver, spleen and abdominal wall, adenopathy and distant tumor metastases. MRI provides good resolution, but requires longer scan times during which respiratory motion and bowel peristalsis can blur images. PET scans may be useful and provide functional imaging, although without high resolution. However, PET-CT may be able to preserve the high resolution of CT and at the same time provide functional imaging. Dr Premkumar stressed the fact that the diffuse spread of peritoneal mesothelioma makes it difficult to do accurate tumor measurements.

Dr Victor Roggli (Duke University Medical Center, USA) spoke about the pathologic features of malignant peritoneal mesothelioma. He mentioned that the peritoneum is the second most common site for malignant mesothelioma, accounting for 10% of cases in his series. The histologic spectrum is the same as for pleural mesothelioma, although pure sarcomatoid variant is much less common in the peritoneum. Malignant mesothelioma must be differentiated from other adenocarcinomas and immunohistochemistry can be helpful to make this distinction. Mesotheliomas usually stain positive for calretinin, cytokeratins 5/6, WT-1, thrombomodulin, and mesothelin but negative for the

adenocarcinoma markers CEA, Leu-M1, Ber-Ep4, B72.3, Bg8, and MOC-31. Electron microscopy can be helpful in making the diagnosis in difficult cases. Dr Roggli mentioned that asbestos is the most widely recognized etiologic factor for peritoneal mesothelioma. In his series, fiber analysis studies show that 75% of peritoneal mesotheliomas in men are asbestos-related, whereas only 33% of cases in women show an elevated lung fiber content [9]. The main fiber type implicated in the USA is amosite whereas chrysotile has not been convincingly shown to cause peritoneal mesothelioma.

The second pathologist to speak in this session was **Dr Andrew Churg (University of British Columbia, Canada)** who talked about the difficulties in separating benign from malignant mesothelial proliferations [10]. He explained that the best guide to making this separation is true stromal invasion into the fat of the chest wall or peritoneum, or the underlying organs. However, he cautioned that invasion must be differentiated from entrapment, a common occurrence in the serosal membranes particularly in areas of active inflammation. Dr Churg also discussed well-differentiated papillary mesothelioma, a lesion of uncertain but generally benign biologic behavior [11]. These tumors have a distinct papillary growth pattern and do not invade the underlying stroma. Well-differentiated papillary mesotheliomas must be separated from ordinary diffuse malignant mesothelioma that have focal papillary architecture.

surgical management of peritoneal mesothelioma

This session was chaired by **Dr Karen Antman (National Cancer Institute, USA)** and **Dr James Pingpank (National Cancer Institute, USA)** and included presentations by speakers who have pioneered surgical approaches for this disease.

Dr Paul Sugarbaker (Washington Hospital Center, USA) described his group's approach to treating this disease. This includes cytoreductive surgery to remove all tumors as well as peritonectomy followed by hyperthermic peritoneal perfusion with cisplatin and doxorubicin [12]. Dr Sugarbaker discussed the potential advantages of this approach including administering chemotherapy before adhesion develop that can limit distribution of chemotherapeutic agents. Also hyperthermia has been shown to have direct tumoricidal activity and can enhance the cytotoxicity of chemotherapy. The overall median survival of 68 patients with peritoneal mesothelioma treated at the Washington Hospital between 1989 and 2003 was 67 months with a projected 3-year survival rate of approximately 64%. In their series female patients had a longer median survival and the results were also better in patients with epithelial and cystic forms of the disease. Resulting morbidities include bile leak, small bowel fistulas, and bleeding. Older patients, especially past age 70, experience an increased morbidity from the treatment. Dr Sugarbaker felt that this aggressive approach for the treatment of peritoneal mesothelioma has resulted in improved overall survival compared to previously published reports.

Dr Richard Alexander (National Cancer Institute, USA) presented the NCI experience in treating peritoneal

mesothelioma. The NCI has pursued a regimen involving laparotomy, surgical removal of tumor and diseased organs, and continuous hyperthermic peritoneal perfusion of cisplatin administered for 90 min. This is followed by early post-operative intraperitoneal administration of paclitaxel and 5-fluorouracil. In a cohort of 49 patients treated in this fashion at a median follow-up of 28 months, median overall survival was 92 months [13]. The main factors associated with survival were age less than 60 years, residual tumor masses at the end of cytoreductive surgery less than 1 cm and a history of previous surgical debulking. Dr Alexander also mentioned that their group has looked at quality of life (QOL) measures in these patients. Their results showed that while the physical scores were lower at 6 weeks after treatment, reflecting the impact of the surgical procedures on QOL, these measures showed a significant and sustained improvement over baseline after 3 months throughout the study.

Dr Daniel Coit (Memorial Sloan-Kettering Cancer Center, USA) provided a third piece of evidence for the benefits of surgical debulking for peritoneal mesothelioma. His group performed a retrospective review of natural history, treatment, and outcome for 37 patients with peritoneal mesothelioma treated at their institution between 1982 and 2002. Of these 37 patients 62% underwent >75% debulking and 81% received some form of chemotherapy, most commonly intraperitoneal chemotherapy. The estimated median survival of these patients was 58 months. The only factors independently associated with improved survival were the ability to achieve at least a 75% debulking and male gender. Dr Coit felt that these results were comparable to other reported series in which more aggressive surgical debulking and hyperthermic intraoperative peritoneal perfusion have been used. Based on these observations, he concluded that it is more likely the biology of the disease, rather than the intensity of the treatment, that determines outcome in these patients.

medical management of peritoneal mesothelioma

The session regarding the medical management of peritoneal mesothelioma was chaired by **Dr Robert Kreitman (National Cancer Institute, USA)** and **Dr Julie Brahmer (Johns Hopkins University, USA)**.

The session started with an introduction by **Dr Claire Verschraegen (University of New Mexico, USA)** regarding the natural history of peritoneal mesothelioma and how this influences treatment decisions. She mentioned that in addition to the symptoms of abdominal pain, distension and ascites peritoneal mesothelioma can be associated with hypoalbuminemia, night sweats, inguinal and umbilical hernia, and hypercoagulability. Laboratory investigations show an increased platelet count in about 50% of patients and many patients also have elevation of the tumor marker CA-125. Dr Verschraegen mentioned that for all mesotheliomas, single-agent general chemotherapy has a response rate of 10 to 15% while as combination chemotherapies improve the response rate to about 25%. A new drug combination such as cisplatin plus pemetrexed that

have shown promise in pleural mesotheliomas may also be effective in peritoneal mesothelioma [14]. Immunotherapeutic agents such as interferon and various cytokines may have a role in treating this disease especially when the amount of disease is minimal [15].

Dr Robert Taub (Columbia University, USA) presented data regarding their multimodality approach for treating this disease. Eligibility criteria for patients to go on their protocol includes a histologic diagnosis of peritoneal mesothelioma, lack of mesothelioma in the chest, good performance status, no prior abdominal radiotherapy, and no more than two prior systemic chemotherapies or one prior intraperitoneal chemotherapy. The treatment protocol includes surgical debulking followed by intraperitoneal administration of cisplatin, doxorubicin and gamma interferon, second laparotomy with attempted resection of any residual disease and intraoperative hyperthermic perfusion with cisplatin and mitomycin followed subsequently by whole abdominal radiotherapy [16]. The median overall survival of the 27 patients treated in this study was 68 months. Dr Taub mentioned that this cohort of patients included four patients with the sarcomatoid form of peritoneal mesothelioma, who died at a mean of 4 months and for whom the treatment had essentially no effect.

Dr Petr Hausner (University of Maryland, USA) suggested that peritoneal mesotheliomas could originate in the omental or mesenteric milky spots. The milky spots are small specialized accumulations of macrophages, T and B lymphocytes formed around postcapillary venules connected by lymphatics and covered by leaky mesothelial cells. Possibly evolutionary predecessors of lymph nodes, these milky spots may also be associated with mesothelioma metastases [17]. Dr Hausner felt that the study of milky spots could increase our understanding of mesothelioma origin and metastases and lead to new therapeutic strategies.

Dr Hedy Kindler (University of Chicago, USA) spoke about novel agents that are currently undergoing evaluation for the treatment of mesothelioma. These include drugs targeting molecular pathways such as signal transduction or angiogenesis [18]. Dr Kindler described ongoing clinical trials in mesothelioma of ZD1839 (Iressa, AstraZeneca) that inhibits epidermal growth factor receptor (EGFR), and imatinib mesylate (Gleevec, Novartis Pharmaceuticals) an inhibitor of the tyrosine kinases associated with platelet derived growth factor (PDGF) receptor, *c-kit* and *Bcr-Abl*. Dr Kindler next talked about clinical trials of drugs targeting the vascular endothelial growth factor (VEGF), a growth factor that appears to play an important role in mesothelioma biology. She described the three VEGF inhibitors in clinical trials for mesothelioma including SU5416, thalidomide and bevacizumab. Of these agents bevacizumab (Avastin, Genentech) an anti-VEGF monoclonal antibody is being evaluated in a randomized Phase II trial of gemcitabine plus cisplatin with bevacizumab or placebo with time to disease progression as the primary endpoint of this trial. The results of this trial will be important to determine if bevacizumab improves the outcome of patients with mesothelioma similar to that seen for other solid tumors using a combination of chemotherapy and bevacizumab.

clinical and pre-clinical evaluation of novel treatments for mesothelioma

The final session of this meeting dealt with pre-clinical and clinical evaluation of novel agents for mesothelioma treatment and was chaired by **Dr Ira Pastan (National Cancer Institute, USA)** and **Dr Jeffrey Schlom (National Cancer Institute, USA)**.

Dr Raffit Hassan (National Cancer Institute, USA), talked about targeting mesothelin for mesothelioma therapy. He explained that mesothelin is a cell surface protein that is highly expressed in mesotheliomas and is a good target for cancer therapy given its limited expression in normal tissues. They have developed a recombinant anti-mesothelin immunotoxin, SS1P, which is currently being tested in Phase I clinical trials [19]. Dr Hassan then provided an update of this study and mentioned that a total of 25 patients including 8 patients with peritoneal and 5 patients with pleural mesothelioma have been treated thus far. The treatment has been well tolerated and shows promising clinical activity including resolution of ascites and stable disease in several patients. After completion of this Phase I study they plan to conduct Phase II studies of SS1P either alone or in combination with chemotherapy in mesothelioma.

Dr Masanori Onda (National Cancer Institute, USA) presented data about the isolation of new monoclonal antibodies (Mab MN and Mab MB) directed against mesothelin. These antibodies, which react with different epitopes on the mesothelin protein, appear to be very useful for detecting mesothelin by immunohistochemistry, fluorescence-activated cell sorting, Western blotting and ELISA. Dr Onda felt that these antibodies could be valuable reagents to study mesothelin function as well as potentially useful for immunotherapy of mesothelin expressing tumors.

The next speaker in this session **Dr Luciano Mutti (Local Health Unit 11 Vercelli, Italy)** talked about his work to identify new targets for mesothelioma therapy such as their studies involving the PI3K/AKT and the nuclear factor (NF)- κ B signaling pathways. He described their *in vitro* models showing that SV40 activates the cell survival pathway PI3K/AKT, whereas asbestos can activate the NF κ B pathway. Dr Mutti also presented data from their laboratory showing that several inhibitors of PI3K/AKT currently being tested and bortezomib that blocks NF κ B activation could be potentially useful for the treatment of mesothelioma [20].

Dr Daniel Sterman (University of Pennsylvania, USA) described their work on cancer gene therapy for mesothelioma. Their group developed a recombinant, replication incompetent adenovirus (Ad) expressing the herpes simplex thymidine kinase (HSVtk) gene that showed *in vitro* and *in vivo* efficacy in animal models of mesothelioma. Subsequently, they have been conducting clinical trials in patients with pleural mesothelioma using intrapleural injection of Ad.HSVtk [21]. Their clinical results show that this treatment is safe and well tolerated. They observed a number of clinical responses in their patients including two long-term survivors who are more than 5 years from their initial therapy and have received no treatment since. Dr Sterman speculated that induction of antitumor response by

Ad.HSVtk may be partly responsible for the efficacy of this therapy. He also mentioned that their group is currently conducting clinical trials of gene transfer using an adenovirus encoding the cytokine IFN- β with the goal of inducing both tumor cell death as well as augmenting natural and T-cell antitumor immune response.

The last speaker in this session **Dr Ronald Kennedy (Texas Tech University Health Sciences Center, USA)** presented his studies regarding the simian virus 40 (SV40) viral oncoprotein, large tumor antigen (Tag). SV40 is an oncogenic DNA virus that has been associated with various human malignancies including mesothelioma. He mentioned their laboratory has developed an *in vivo* murine experimental pulmonary metastasis model to assess tumor immunity based upon vaccination strategies utilizing SV40 Tag as the target antigen [22]. Their studies have demonstrated that both the recombinant protein as well as plasmid DNA immunization provides complete tumor immunity within this experimental pulmonary metastasis model. Tumor immunity was associated primarily with antibody response following recombinant SV40 Tag immunization with a CD8+CTL response following plasmid DNA immunization. Dr Kennedy felt that such strategies represent a promising area of research for mesothelioma treatment and should be further investigated in light of the potential for antigen cross-presentation and epitope spreading.

summary

This meeting provided an opportunity for experts in mesothelioma research and treatment to focus specifically on peritoneal mesothelioma. The proceedings of this meeting should be a useful resource to physicians and patients to get the latest information on the management of this disease. We also feel that this meeting will lead to regular scientific meetings and workshops focused on peritoneal mesothelioma resulting in improved understanding and treatment of this disease.

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references

1. Spirtas R, Heineman EF, Bernstein L et al. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 1994; 51: 804–811.
2. Price B, Ware A. Mesothelioma trends in the United States: an update based on surveillance, epidemiology, and end results program data from 1973 through 2003. *Am J Epidemiol* 2004; 159: 107–112.
3. Pass HI, Liu Z et al. Gene expression profiles predict survival and progression of pleural mesothelioma. *Clin Cancer Res* 2004; 10: 849–859.
4. Robinson BW, Creaney J, Lake R et al. Mesothelin-family proteins and diagnosis of mesothelioma. *Lancet* 2003; 362: 1612–1616.
5. Selikoff U, Hammond EC, Seidman H et al. Mortality experience of insulation workers in the United States and Canada, 1943–1976. *Ann NY Acad Sci* 1979; 330: 91–116.
6. Maurer R, Egloff B. Malignant peritoneal mesothelioma after cholangiography with thorotrast. *Cancer* 1975; 36: 1381–1385.
7. Metintas S, Metintas M, Ugun I, Oner U. Malignant mesothelioma due to environmental exposure to asbestos: follow-up of a Turkish cohort living in a rural area. *Chest* 2002; 122: 2224–2229.
8. Whitley NO, Brenner DE, Antman KH et al. CT of peritoneal mesothelioma: analysis of eight cases. *Am J Roentgenol* 1982; 138: 531–535.
9. Roggli VL, Sharma A, Butnor KJ et al. Malignant mesothelioma and occupational exposure to asbestos: a clinicopathologic correlation of 1445 cases. *Ultrastruct Pathol* 2002; 26: 55–65.
10. Chung A, Colby TV, Cagle P. The separation of benign and malignant mesothelial proliferations. *Am J Surg Pathol* 2000; 24: 1183–1200.
11. Daya D, McCaughey WT. Well-differentiated papillary mesothelioma of the peritoneum. A clinicopathologic study of 22 cases. *Cancer* 1990; 65: 292–296.
12. Sugarbaker PH, Welch LS, Mohamed F, Glehen O. A review of peritoneal mesothelioma at the Washington Cancer Institute. *Surg Oncol Clin N Am* 2003; 12: 605–621.
13. Feldman AL, Libutti SK, Pingpank JF et al. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. *J Clin Oncol* 2003; 21: 4560–4567.
14. Vogelzang NJ, Rusthoven JJ, Symanowski J et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003; 21: 2636–2644.
15. Freedman RS, Vadhan-Rai S, Butts C et al. Pilot study of Flt3 ligand comparing intraperitoneal with subcutaneous routes on hematologic and immunologic responses in patients with peritoneal carcinomatosis and mesotheliomas. *Clin Cancer Res* 2003; 9: 5228–5237.
16. Taub RN, Keohan ML, Chabot JC, Fountains, Plitts M. Peritoneal mesothelioma. *Curr Treat Options Oncol* 2000; 1: 303–312.
17. Krist LF, Kerremans M, Broekhuis-Fluitsma DM. Milky spots in the greater omentum are predominant sites of local tumour cell proliferation and accumulation in the peritoneal cavity. *Cancer Immunol Immunother* 1998; 47: 205–212.
18. Kindler HL. Moving beyond chemotherapy: novel cytostatic agents for malignant mesothelioma. *Lung Cancer* 2004; 45S: S125–S127, 2004.
19. Hassan R, Bera T, Pastan I. Mesothelin: a new target for immunotherapy. *Clin Cancer Res* 2004; 10: 3937–3942.
20. Sartore-Bianchi A, Nici L, Porta C, Chatterjee D, Mutti L, Calabresi P. The combination of the novel camptothecin analogue Gimatecan (ST1481) plus the proteasome inhibitor PS341 produces an enhanced pro-apoptotic effect in a malignant mesothelioma cell line. *Proc Am Assoc Cancer Res* 2003; 44: 742 (Abstr R729).
21. Serman DH, Treat J, Litzky LA. Adenovirus mediated herpes simplex virus thymidine kinase gene delivery in patients with localized malignancy: results of a phase I clinical trial in malignant mesothelioma. *Hum Gene Ther* 1998; 9: 1083–1092.
22. Watts AM, Shearer MH, Pass HI, Bright RK, Kennedy RC. Comparison of simian virus 40 large T antigen recombinant protein and DNA immunization in the induction of protective immunity from experimental pulmonary metastasis. *Cancer Immunol Immunother* 1999; 47: 343–51.